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14. ABSTRACT

Individuals with germline mutations in BRCA1 have an elevated but incomplete risk of developing ovarian cancer suggesting the presence of genetic modifiers of ovarian cancer in this population. A genome wide association study (GWAS) for ovarian cancer in BRCA1 mutation carriers has identified several novel modifiers of ovarian cancer risk for BRCA1 mutation carriers that can be used for individualized ovarian cancer risk assessment.

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Introduction:

Inactivating mutations in the *BRCA1* tumor suppressor gene have been detected in approximately 10% of all ovarian cancers. Individuals with germline mutations in *BRCA1* have a substantially increased risk of developing ovarian cancer as compared to the general population, with an estimated cumulative risk of ovarian cancer by age 70 of 39%. These findings indicate that although *BRCA1* mutation carriers are at high risk for developing ovarian cancer, a sizeable proportion of women who carry a deleterious mutation will not develop this disease. In addition, the findings show that there is considerable variation in the age of onset of ovarian cancer in this population. This variable penetrance and age of onset of ovarian cancer suggest that there are additional genetic and environmental factors that modify the age specific risk of ovarian cancer for *BRCA1* mutation carriers. Common genetic variants that are associated with the risk of ovarian cancer have recently been identified through candidate gene and genome wide association studies in the general population. This suggests that common genetic variants may also modify ovarian cancer risk in carriers of *BRCA1* mutations. Identification of these genetic risk factors may prove useful for identifying those *BRCA1* carriers at elevated or lowered risk of ovarian cancer compared to the average *BRCA1* carrier. Women at increased risk may subsequently benefit from enhanced screening or certain prevention measures such as prophylactic oophorectomy, whereas women at lowered risk may be able to avoid these types of intervention. Thus, we proposed a study aimed at identifying genetic risk factors for ovarian cancer in BRCA1 mutation carriers through a genome wide association study in BRCA1 mutation carriers. The overall intent was to complete a genome wide association study of *BRCA1* carriers, validate candidate risk modifiers, to assess the contribution of these modifiers to sporadic ovarian cancer and to develop risk prediction models.

Body

Aim 1: To conduct a genome-wide association scan in 1,000 *BRCA1* carriers with ovarian cancer and 1,000 age-matched unaffected *BRCA1* carriers.

As outlined in detail in our previous annual report, we recently conducted a GWAS of *BRCA1* mutation carriers diagnosed with ovarian cancer. In collaboration with Drs. Douglas Easton and Antonis Antoniou at the University of Cambridge, we evaluated associations with both breast and ovarian cancer using a retrospective likelihood model. For ovarian cancer, 10 SNPs exhibited associations of $p<1 \times 10^{-5}$ and 37 had associations of $p<1 \times 10^{-4}$. Interestingly, rs1339552 on chromosome 9 in BCN2 and rs7651446 from TIPARP on chromosome 3 found to exhibit genome wide associations with ovarian cancer in the general population also showed highly significant associations ($p=1.9\times10^{-5}$ and $p=1.7\times10^{-4}$, respectively) with ovarian cancer in *BRCA1* mutation carriers. These loci can be considered genetic risk factors for ovarian cancer in *BRCA1* mutation carriers. These efforts completed the proposed studies in Aim, which include Task 1-4.

Aim 2: To further evaluate observed associations between ovarian cancer risk and SNPs implicated in Aim 1 by genotyping 1,500 *BRCA1* ovarian cancer cases and 1,500 unaffected *BRCA1* carriers.

GWAS validation studies

In our previous annual report we described our involvement in the iCOGS study of 211,000 candidate SNPs, which included 35,000 candidate SNPs from the *BRCA1* GWAS including 6,000 from the *BRCA1* Ovarian Cancer GWAS. Genotyping data from the original GWAS and the iCOGS study were available from 9866 unaffected BRCA1 mutation carriers and 1839 affected with ovarian cancer. A total of 62 SNPs in 17 regions were associated with ovarian cancer risk for *BRCA1* carriers at $P<10^{-4}$. These included SNPs in the BNC2 9p22 and 3q25 loci previously associated with ovarian cancer risk in both the general population and *BRCA1* carriers. Associations ($P<0.01$) with ovarian cancer risk were also observed for SNPs in three other known ovarian cancer susceptibility loci (8q24, 17q21, 19p13), but not 2q31. After excluding SNPs from known ovarian cancer susceptibility regions, there were 48 SNPs in 15 regions with $P=5\times10^{-7}$ to 10^{-4}. Five SNPs from four of these loci were genotyped in additional stage 3 samples (2,204 unaffected, 442 with ovarian cancer). In the combined stage 1-3 analyses, SNPs rs17631303 and rs183211 ($r^2=0.68$) on chromosome 17q21.31 had P-values for association of 1×10^{-8} and 3×10^{-8} respectively, and rs4691139 at 4q32.3 had a P-value of 3.4×10^{-8}. None of these

SNPs were associated with breast cancer in BRCA1 mutation carriers. Imputation using data from the 1000 Genomes Project, identified several SNPs in 17q21.31 with stronger associations than the most significant genotyped SNP in the combined *BRCA1/2* analysis (rs169201, $P=6.24\times10^{-11}$). The most significant SNP (rs140338099 (17-44034340), $P=3\times10^{-12}$) located in *MAPT*, was highly correlated ($r^2=0.78$) with rs169201 in *NSF*. This locus appears to be distinct from a previously identified sporadic ovarian cancer susceptibility locus located >1Mb distal on 17q21 (spanning 43.3-44.3Mb, build 36.3). Analysis of associations with variants identified through 1000 Genomes Project based imputation of the Stage 1 and 2 samples, also revealed 19 SNPs with stronger evidence of association ($P=5.4\times10^{-7}$ to 1.1×10^{-6}) than rs4691139 on 4q32.3. All were highly correlated (pairwise $r^2>0.89$) and the most significant (rs4588418) had $r^2=0.97$ with rs4691139. No association was found between rs4691139 and ovarian cancer risk in the general population based on data by the Ovarian Cancer Association Consortium (OCAC) in 18,174 cases and 26,134 controls (Odds Ratio=1.00, 95%CI:0.97-1.04, P=0.76). Based on these efforts we have completed Tasks 5 to 9 from Aim 2.

Aim 3: To evaluate risk modifiers from the *BRCA1* breast cancer GWAS and risk factors from sporadic ovarian cancer GWAS as modifiers of ovarian cancer in *BRCA1* carriers.

To improve statistical power to identify ovarian cancer risk loci for BRCA1 mutation carriers, a meta-analysis of association test results from the BRCA1 iCOGS (12,790 unaffected; 2,462 affected) and OCAC iCOGS (18,174 EOC cases; 26,134 controls) studies was conducted. Six new genome wide significant loci were identified through this process including: rs3820282 in WNT4 ($p=2.0 \times 10^{-8}$); rs12039431 RSPO1 ($p=1.44 \times 10^{-11}$); rs17329882 in SYNPO2 ($p=1.95 \times 10^{-8}$); rs115344852 in GPX5 ($p=3.15 \times 10^{-8}$); 136138765 in ABO ($p=1.95 \times 10^{-8}$); rs8044477 in GOT2 ($p=1.0 \times 10^{-8}$). All were novel associations that also showed significance ($p<0.05$) in BRCA1 carriers alone. This effort substantially increased the number of risk loci for ovarian cancer in BRCA1 mutation carriers. We previously reported that variants from the 19p13.1 locus were associated with ovarian cancer risk in a genotyping study of 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers, which included 1,465 *BRCA1* mutation carriers and 453 *BRCA2* mutation carriers with ovarian cancer. The rs67397200 SNP at 19p13.1 was strongly associated with ovarian cancer risk in *BRCA1* (HR=1.16; 95%CI 1.05-1.29; $p=3.8\text{x}10^{-4}$) and *BRCA2* (HR=1.30; 95%CI 1.10-1.52; $p=1.8\text{x}10^{-3}$) mutation carriers. This SNP and others in this locus were also associated with breast cancer risk in *BRCA1* mutation carriers. To fine map the 19p13.1 locus in an effort to identify the causative variants in this region a meta-analysis of results from the OCAC and BRCA1 ovarian cancer studies and the BCAC and BRCA1 breast cancer studies using 1000 Genomes imputed SNP was conducted. Results show that SNPs in the ANKLE1 locus on 19p13.1 appear to drive the association with breast and ovarian cancer (Table 1).

Table 1 Most significant associations for SNPs in a meta-analysis of breast and ovarian cancer studies

MarkerName	P.value	LOCATION	Direction	bcac_snpname	position	bcac_pval	brca1_pval	ocac_pval
17390291_T_C	1.55E-26	BABAM1	--	rs4808075	17390291	4.42E-13	4.77E-15	9.17E-20
17390917_G_C	8.34E-23	ANKLE1	--	rs4609972	17390917	4.42E-10	1.10E-14	5.93E-14
17391328_G_A	2.70E-26	ANKLE1	++	rs10419397	17391328	6.57E-13	5.55E-15	1.29E-19
17392894_G_A	1.04E-23	ANKLE1	--	rs8100241	17392894	1.28E-10	5.11E-15	8.66E-14
17393530_T_A	4.02E-23	ANKLE1	--	rs8108174	17393530	2.15E-10	1.23E-14	7.16E-14
17393925_C_A	5.26E-27	ANKLE1	++	rs56069439	17393925	2.22E-13	3.33E-15	1.94E-19
17394124_T_G	9.52E-24	ANKLE1	++	rs2363956	17394124	1.31E-10	4.44E-15	5.75E-14
17395401_C_T	5.59E-27	ANKLE1	++	rs4808076	17395401	2.90E-13	2.55E-15	3.72E-19
17396942_C_T	3.48E-23	ANKLE1	--	rs748850	17396942	1.84E-10	1.27E-14	5.47E-14
17398085_C_A	6.07E-27	ANKLE1	++	rs111961716	17398085	2.63E-13	3.22E-15	6.97E-19
17399625_T_C	2.12E-23		++	rs11668840	17399625	1.86E-10	6.99E-15	9.40E-14
17400765_T_C	4.22E-27		--	rs113299211	17400765	2.40E-13	2.33E-15	8.13E-19
17401521_C_T	7.66E-23		--	rs12974508	17401521	1.40E-10	4.30E-14	1.23E-13
17401859_G_A	7.31E-28		++	c19_pos17262859	17401859	1.27E-13	7.77E-16	1.14E-18
17404072_T_A	2.81E-27	ABHD8	++	rs55924783	17404072	1.61E-13	2.44E-15	1.35E-18
17406167_C_T	4.55E-27	ABHD8	++	rs28473003	17406167	2.80E-13	2.11E-15	3.43E-18
17407695_G_T	2.06E-26	ABHD8	++	rs13343778	17407695	3.92E-13	7.44E-15	3.18E-18
17409380_C_T	4.08E-22	ABHD8	--	rs12982058	17409380	8.63E-10	2.90E-14	5.14E-13
17409671_C_T	2.56E-25	ABHD8	++	rs10424198	17409671	1.18E-12	3.13E-14	3.85E-18

These studies complete Task 10. Additional studies addressing Tasks 11-13 are underway as outlined in a recently approved no cost extension for this award.

Key Research Accomplishments

- Completed a validation study of candidate ovarian cancer risk modifiers for *BRCA1* mutation carriers.
- Verified three known ovarian cancer risk factors as ovarian cancer risk modifiers for *BRCA1* mutation carriers
- Identified novel ovarian cancer risk modifier loci for *BRCA1* mutation carriers on chromosome 4q32 and 17q21.
- Identified six new ovarian cancer susceptibility loci in a meta-analysis of BRCA1 and sporadic ovarian cancer studies.

Reportable Outcomes

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Conclusion

In summary, we have completed the discovery and validation phases of an ovarian cancer GWAS for *BRCA1* mutation carriers. We verified that variants from five loci that have been associated with risk of ovarian cancer in the general population are risk modifiers of ovarian cancer for *BRCA1* mutation carriers. In addition, two novel loci at 4q32 and 17q21 were associated with ovarian cancer risk in *BRCA1* carriers. Of these the 4q32 locus was not associated with ovarian cancer in *BRCA2* mutation carriers or the general population. Thus, specific modifiers of ovarian cancer risk exist for this population. Six novel ovarian cancer risk loci were also observed by combining results from BRCA1 and sporadic ovarian cancer studies. The 13 risk modifiers of ovarian cancer risk are useful for predicting differences in individual ovarian cancer risk among *BRCA1* mutation carriers. Ongoing genotyping of other candidate variants are expected to be useful for improved risk assessment of ovarian and breast cancer risk for *BRCA1* and perhaps *BRCA2* mutation carriers.